THE BIOLOGY OF TUMOURS

C. MANSELL MOULLIN

THE BIOLOGY OF TUMOURS

THE BIOLOGY OF TUMOURS

BY

C. MANSELL MOULLIN, M.A., M.D.Oxon., F.R.C.S.

LT.-COL. R.A.M.C. (T.); CONSULTING SURGEON TO THE LONDON HOSPITAL; LATE VICE-PRESIDENT ROYAL COLLEGE OF SURGEONS; FELLOW OF PEMBROKE COLLEGE AND RADCLIFFE TRAVELLING FELLOW, OXFORD

H. K. LEWIS & CO. LTD.
136 GOWER STREET, LONDON, W.C.
1916

PREFACE

My object in these pages has been to deal with the biology of tumours more thoroughly than I could in the Bradshaw Lecture which I had the honour of delivering before the Royal College of Surgeons in 1912, and to place their origin and classification upon a scientific basis.

The conclusions at which I have arrived differ in many particulars from the views that are current generally, and must therefore expect to meet with a good deal of adverse criticism. Time will tell. In science, at least, orthodoxy is only the doxy of the day.

C. Mansell Moullin.

CONTENTS

CLASS I

CLASS II

INTRODUCTION

Tumours are divided by their mode of origin into two classes. One of these is due to the sudden awakening of the innate reproductive power of the tissues, in virtue of which they give birth to buds that grow into tumours. The other is due to details of structure not being carried out as completely as they ought to be.

I. Tumours due to the Reproductive Power of the Tissues

The distinguishing feature of these tumours is their independence. They are independent growths, leading their own lives, so far as they can, and are the offspring of the tissues from which they grow, belonging not to the same generation as the parent, but to the succeeding one.

The development of the individual is an epitome of that of the race. This is true not only of

the individual, but of the tissues that compose it. All tissues in the course of their formation pass through the stages through which their ancestors passed in the evolution of the race, compressed beyond recognition. If the development of a tissue is arrested at one of those stages, before it has reached its final form, that tissue retains and can exercise the same powers that the corresponding ancestor once possessed.

One of these powers is that of direct asexual reproduction. The simpler organisms possess this power in full. It is their only method of reproduction, and all living things descended from them inherit this power in greater or less degree.

In the more highly organised animals this method of reproduction is superseded by another more efficient. They never make use of it, and its range of action gradually diminishes, but the power itself does not die out or disappear. It lies dormant, so much of it as persists, and if conditions become favourable it is capable of asserting itself at any moment.

So long as development continues to be normal, there is no opportunity for it. The germ cells have given it up and are wholly engaged with the other method. The somatic cells are told off for other duties and are not concerned with reproduc-

tion at all. But if the course of development is arrested, so that some of the tissues remain on a plane that was normal for their remote ancestors, those tissues are able to exercise this power with the same energy that those ancestors could, and, if the arrest takes place sufficiently early, can give off buds capable of independent growth in the same way that those ancestors did. The arrest of development furnishes the opportunity. When once development has been arrested, all that is necessary is the presence of some stimulus, mechanical or chemical, to rouse the latent reproductive power into activity.

Development, like growth, is the result of chemical changes in the tissues, changes that are taking place at the present time added to the accumulated results of all those that have taken place in former generations. Anything that interferes either with the inheritance of the products of past chemical changes, or with the working of recent ones, interferes with development and may arrest it.

The structure of the tumours that are due to the awakening of the reproductive power of the tissues depends upon that of the parent stem; their rate of growth upon the maturity of the parent cell at the moment it gave off the tumour

bud ; and the degree of their organisation upon the stage in the life-history of the race the parent cell had reached when its development was arrested.

II. Tumours due to Structural Details not being perfectly carried out

Development implies not only the progressive advance of structures that are of use, but no less also the disappearance of those that have ceased to be of use. Failure in either of these directions while growth continues may lead to the formation of a tumour, which, however, is only an abnormal development of part of the parent body, not the product of a fresh bud endowed with the power of independent growth.

THE BIOLOGY OF TUMOURS

It does not seem to me that it is either necessary or profitable in a work of this kind to attempt a definition of the word "tumour." The structures to which I refer are the growths, familiar to every one, that so frequently make their appearance among the normal tissues of the body, imitating them more or less in texture, draw all their nourishment from them, recognise no limits of size or shape, and never serve a useful purpose of any kind. They are rarest in that period in which development is most active. In adult life they occur more frequently. As the tissues grow old they become more and more common, until in the aged they can often be counted by the score.

Classification.—The variety of these growths makes their classification difficult. No method hitherto suggested can be said to meet all the requirements. The division into simple and malignant, for instance, is convenient, for it furnishes

a good working rule in practice, where an opinion to be of any value must be dogmatic, but as a classification it cannot be upheld. There is no such thing as a separate class of malignant growths. No distinguishing line can be drawn between them and other growths. Malignancy is an occasional feature of all classes of tumours, even of those that enjoy the best reputation; and it is not uncommon for a tumour to all appearance non-malignant, to increase slowly in size for years, or even to remain stationary for a time, and then suddenly to change its character and destroy life in the course of a few months. Nor is there any fixed standard of malignancy. It varies in degree even among tumours that appear to be alike. Malignancy is a clinical feature, and clinical features do not provide a good basis for the classification of pathological growths.

Classification by structure promises better. Broad general lines can be drawn, and many groups of tumours can be separated from the rest. In other instances, however, the structural details are so varied and complex that general agreement seems to be almost impossible. Classification by origin is better still, but unhappily the basis usually chosen, the three germinal layers of the embryo, is not sufficiently exact. The layers are

not all of equal value, and they do not remain distinct from each other, so that it very soon becomes impossible to make certain to which of them a particular growth should be assigned.

The most satisfactory basis for classification is the mode of origin. Tumours are due either to the reproductive power that is innate in all living tissues being suddenly roused into activity; or to changes that occur in the course of development being imperfectly carried out. These two classes must be considered separately, though there is reason to think that the same cause may underlie them both.

CLASS I

TUMOURS DUE TO THE REVIVAL OF THE PRIMITIVE POWER OF ASEXUAL REPRODUCTION. GEMMATION TUMOURS

This group includes the vast majority of tumours, simple and malignant, both those that grow from the generative cells and those that grow from the other tissues of the body.

It does not include structures that are formed as a result of fission or division. These are not tumours in the strict sense of the term. Unless

prevented by mechanical conditions, the parts into which they divide develop equally. A fertilised ovum, for example, or, where reproduction is still unicellular, a growing bud, may increase in size so fast that any slight accident or movement is enough to cause the primary segments to separate from each other. If the separation is complete and the other conditions are favourable, two distinct organisms are produced, resembling each other so closely that even late in life they cannot always be distinguished—as in the well-known instance of the two poachers who, although they had been convicted, one it is believed thirty-nine times and the other fifty-three, were yet a hopeless puzzle to the village constable and the Bench. If the separation is incomplete the result is one of those double monstrosities so common in our museums, which sometimes are born alive and even reach old age. The same thing is true of bifid limbs and other organs. They originate in the same way, at a later stage, as the products of overgrowth of normal structures or of too rapid growth. Sometimes when one part is developed fully and the other remains stunted and atrophied, it is not easy to recognise the relation they bear to each other; but, as Bland Sutton has pointed out, their origin can always be ascertained by their similarity at

the point of division. Structures such as these should be placed in a class by themselves. They differ from what are commonly called tumours in one essential particular—development proceeds normally except in so far as it is impeded by pressure or other mechanical causes.

The characteristic feature of gemmation tumours —that which distinguishes them from others and from the structures from which they grow—is their independence. They are like the buds that grow upon some of the Invertebrata, the Cœlenterata, for example. Their life is not part of the life of the parent organism. They are not able to support themselves, it is true. They are indebted to the parent organism for all that they require in the way of sustenance; but if transplanted to another host, so that they can get supplies equally well, they continue to grow and thrive long after the original parent is dead. They live upon the parent, like a parasite upon its host, drawing all they want from it, doing nothing for it in return, and in some instances draining it of all its strength until it dies of starvation. These tumours are the offspring of the tissues from which they grow. They belong not to the same generation, but to the next.

Structure and Character.—The structure of these

tumours depends upon that of the parent stem. It is never so perfect, but there is always a general resemblance. The character, whether they are malignant or not, depends upon the stage the parent cell has reached when its development is arrested and the tumour bud begins to grow. These tumours may assume many different forms —a form that grows fast, or a form that grows slowly; a form that remains circumscribed and limited, or a form that retains its embryonic characteristics, spreads in all directions and invades other organs. If the parent cell is still in the actively growing embryonic stage at the moment that development is arrested and the bud is given off, the bud will be embryonic too. If, on the other hand, it has nearly reached its perfect form, the bud will increase in size with proportionate slowness, and push surrounding structures to one side instead of invading them. Every organ and every tissue has its own kind of tumour, which resembles it in structure more or less, but which, according to the degree of maturity attained by the parent cell at the moment that the bud is given off, may be benign or malignant, or so evenly balanced between the two that it is impossible to say whether it is one or the other. There is no separate class of malignant tumours;

rapidly growing malignant forms occur in all classes.

Organisation.—The degree of organisation of which these tumours are capable varies within very wide limits. They may develop into organisms almost as complex as the one from which they grew; or into structures composed of well-formed tissues; or they may be mere masses of cells heaped together without order or arrangement. Which of these forms the tumour takes depends upon the stage in the life-history of the race that the parent cell had reached at the moment of the formation of the tumour bud. The individual is the epitome of the race. Each cell as it develops passes through all the stages through which its ancestors passed in the course of evolution, and any bud that is given off by the parent cell in the course of its growth possesses the same powers that a bud growing from the corresponding ancestor would have possessed in days gone by. The bud that springs from the cells of the early embryo, like those that are given off by lowly organised forms of animal life, is able to reproduce the organism more or less perfectly, while one that is only formed when the organism is fully developed is limited to the production of a growth composed of simple tissues.

Direct or Asexual Reproduction

One of the points that distinguish living organisms from inert matter is the power they possess of absorbing and assimilating foreign material, in virtue of which they are able to replace the waste of living, increase in size, and, when the limits of size are reached, increase in number. This power of growth is inherent in all living things so long as they are living. It is born in them with their birth, lives with them throughout their lives, and dies with them when they die. So long as conditions are favourable, it knows no bounds or limits.

All that is true of growth is true also of reproduction, for reproduction is only growth beyond the individual.

In primitive organisms, such as those which existed in that immeasurably remote period when life made its appearance upon earth, this is not difficult to understand. Their structure was of the simplest, and their growth continued until at last their size became so great that they were compelled to divide. The dimensions reached before division took place, probably varied in each case. There was no defined limit. It depended entirely upon circumstances. But when

circumstances continued to be the same for generation after generation, the intervals gradually became more regular and a certain uniformity was introduced. Reproduction took place with regularity as soon as a certain size was reached.

In higher organisms, in the Metazoa, for example, such simplicity of procedure is no longer possible. Increase in size in a multicellular organism necessarily involves division of labour. Different functions have to be assigned to different parts of the body, and, because the existence of the race depends upon it, one of the first to be assigned in this way is the function of reproduction. Certain cells are marked off from the rest at the very earliest moment to act as germ cells, and the whole duty of reproduction is henceforth given up to them. They undertake it all.

The rest of the cells are known as somatic cells. From the moment the germ cells are marked off, these cease to have anything to do with reproduction. They may be able to influence it indirectly through the medium of the germ cells, which depend upon them for all the necessaries of life, but they take no direct share in it. Their mission is to carry out the various kinds of work upon which the life and well-being of the individual depend. The power of reproducing their like is

theirs by inheritance, but so long as conditions are normal they never exercise it, and as they become more and more perfect in their own line of work their capacity for carrying out this special one grows less and less.

In the earliest days, both of the individual and of the race, the distinction between these two groups of cells is not well marked. The cells of one group can still take the place of those of the other and perform all its duties. In the ova of some of the Echinodermata, for example, the germ cells and the somatic cells can be displaced artificially and each will carry on the work of the other. As organisation advances, however, they diverge, and in a little while they become permanently distinct.

This division into germ and somatic cells, founded upon the function of reproduction, is the primary division of the organism. On it is based the classification of the tissues and of the tumours that grow from them. One class of tumours grows from tissues that are given up entirely to the reproduction of the race; the other from tissues that have undertaken other kinds of work and have ceased to exercise the power they originally possessed.

(*a*) **The direct reproductive power of the**

germ cells.—In the simplest forms of life all reproduction from the germ cells is direct. There is no suggestion of a second element, or of sex. How and when it first came about that germs to reproduce the race, instead of growing from a single cell, should require a stimulus coming from a second one to start them on their course, is not known; but it is obvious that germs formed in this way, by the fusion of parts of two cells, would stand a better chance of success in the struggle for existence than those formed from a single cell, if only because of the greater likelihood of the occurrence of useful variations. When this bicellular origin was once initiated, the division of the primitive germ organs into two parts, an ovary and a testis, each providing its own special factor in reproduction; the maturing of the two products at different times, so that the conjunction of two separate individuals would be required, and the comparative weakness of self-fertilisation avoided; and then the suppression of one of these organs in one of the individuals and of the other in the other, with the result of separating the sexes entirely, are such obvious advantages that they follow as a matter of course.

Sexual reproduction, therefore, which bulks so largely in our vision that it has caused the exis-

tence of the primitive method of direct reproduction to be almost ignored, is only a specialisation. The primitive method, the birthright of all living tissues, continues to exist. It does not die out or disappear because sexual organs have been developed. It is still there, though its range of action grows more and more limited, and if occasion requires can be called into play at once. In many insects, for example, generations in all respects identical with those that precede them can be produced asexually even though functional sexual organs are in existence; and in animals so highly specialised as frogs, ova that have never been fertilised by spermatozoa can be made to develop even into the tadpole stage by applying a suitable chemical stimulus. The same thing within narrower limits is true of the germ organ in man. It may not retain sufficient of its original power of direct reproduction to give birth to a new and perfect individual, but in embryonic life at any rate it retains enough to enable it to give off buds capable of growing into highly complex structures; and though as development advances the range and strength of the primitive reproductive power diminish, what is left of it can be called into action at almost any time if a suitable stimulus is applied.

(*b*) **The direct reproductive power of the somatic cells.**—The somatic cells are the complement of the germ cells. The function of the germ cells is the reproduction of the race. That of the somatic cells is the maintenance of the individual. In the simplest forms of life, and in the earliest days of those more complex, the reproductive power of the somatic cells is equal to that of the germ cells. When the somatic cells take up their other duties they cease to make any use of their reproductive power, and, as a consequence, it dwindles away until at last it almost disappears.

The diminution in the reproductive power of the somatic cells can be traced more easily in the evolution of the race than in the development of the individual. The stages are better marked; they have not undergone such a degree of compression. In the simplest forms of animal life the reproductive power of the somatic cells is so strong that, in some of the Cœlenterata, for example, the whole organism can be regenerated from fragments taken from almost any part of the original. Even in such animals as marine worms, some of the body segments can give birth to perfect and complete individuals which become detached and lead separate lives. In more highly organised animals such as Crustacea the reproductive power

is more limited. Only portions of the body and simple structures such as limbs can be reproduced. In Vertebrata it is more limited still. Reproduction of an organ is only possible in a few, such as the Lacertilia; and when organisation has reached the degree of perfection that it has in mammals, reproduction, at any rate in adult life, is confined to the simpler kinds of tissues. The power the somatic cells originally possessed in full has dwindled away with the advance of organisation until at last it is only capable of the reproduction of some of the simplest structures.

The same thing is shown in the development of the individual. In the earliest moments of embryonic existence the power of reproduction enjoyed by the somatic cells is enormous. It is quite possible that some of the included fœtuses that occur in strange parts of the body are really the product of somatic cells in which the reproductive power has not yet had time to deteriorate, rather than of germ cells that have been accidentally displaced; and also that the little buds sometimes met with even in human embryos growing on the site of limbs that have been lost early in uterine life are really attempts at reproduction. But the early stages of the human embryo are abbreviated to such an extent—changes that re-

quired epochs for their production in the evolution of the race being compressed into as many moments in the development of the individual—that the period during which reproduction on such a scale as this is possible lasts but an infinitesimal time. The reproductive power of the somatic cells is more active in the fœtus than in the child, and more active in the child than in the adult, but after the earliest embryonic days are past it is practically limited to the reproduction of the simpler kinds of tissues.

The Classification of Gemmation Tumours

To be exact and logical, tumours that are due to the revival of the primitive reproductive power of the tissues should be divided into three classes —those that spring from the primitive organism before it is differentiated into germ and somatic portions, and those that grow later in life from one or other of these. Such lines of division are, however, impossible. There is no such thing in nature. For a long time after the separation of the germ and somatic cells is apparently complete and final, they can either of them resume and use all the powers they once possessed. The somatic cells, for instance, in many of the lower forms of life

retain the power of producing germs throughout their whole existence though they may never exercise it; and even in comparatively highly organised animals the cells of the ovum can be artificially displaced in such a way that the somatic ones perform all the functions of the germ cells, and *vice versa*. Normal development cannot be divided by hard-and-fast lines into separate stages, nor can the tumours that originate during its course.

It is, therefore, of no use trying to distinguish tumours growing from germ or somatic cells from those that arise in the primitive organism before the primary division has taken place; and in the same way it is of no use trying to separate those that grow from the ovary from those that originate in the germ organ from which the ovary is developed. But this does not hold good of tumours that are formed later in life, after the early embryonic days are past. As development advances, germ cells and somatic cells diverge from each other more and more, and the tumours that spring from them are proportionately distinct. Thus two great groups can be separated from each other except at the point of origin where they touch, and I shall take those that spring from the germ organ and its derivatives, the ovary and testis, first.

(*a*) **Tumours of the germ organ and its derivatives: germ-cell tumours.**—Growths developed asexually from the germ organ or its derivatives occur in many different forms. Nearly all spring either from the germ organ or the ovary. They rarely grow from the testis, at any rate after the sperm cells are developed, probably because of the high degree of specialisation it has attained. The included fœtuses described by Verneuil in connection with the testis are either derived from ovarian rests embedded in the paradidymis as suggested by Bland Sutton, or more probably from persisting fragments of the as yet undifferentiated germ organ.

It is not possible to arrange these tumours in classes. They form a series almost without a break, ranging from included fœtuses at one end to ovarian adenomata, mere heaped-up masses of epithelial cells at the other.

Included fœtuses.—In the earliest days of existence the reproductive power of the germ cells is only paralleled by that of the most primitive organisms. Like these, the germ cells can give off buds capable of growing into organisms almost as elaborate as the parent one. Tumours of this kind are known as included fœtuses. They grow from the germ cells before the generative organs

are differentiated, and occur therefore in both sexes. As a rule they are met with in the genital area. They may, however, occur in distant parts of the body, and then they are due either to the accidental displacement of some of the cells of the germ organ in the course of development, or to the fact that some of the somatic cells have been stimulated into excessive action before their reproductive power has lost any of its primitive vigour.

Internal teratomata.—As the power of direct reproduction diminishes in the course of racial evolution, leaving traces of what it once could do here and there (as where, for instance, generations of certain insects are produced for a time asexually), so too it diminishes in the course of the evolution of the individual. Buds given off by the germ cells in the earliest moments of individual existence grow into structures almost as perfect as the parent. Those formed later, known as internal teratomata, are far less complete. They may be made up of organs presenting a general resemblance to those of the parent, but their structure is imperfect; there is no order in their arrangement, and they are unlike anything else in shape or outline.

Ovarian dermoids and ovarian adenomata.—

No hard-and-fast line can be drawn between internal teratomata and these, which undoubtedly owe their origin to the reproductive power of unfertilised ova, roused into action by some stimulus. There is an unbroken series of tumours, arising as a result of direct reproduction, first from the germ organ and then from the ovary, ranging from the most complex, produced in the earliest moments of individual existence, to the simplest, which often do not make their appearance until old age.

(*b*) **Tumours that grow from somatic cells: somatic-cell tumours.**—There is no difference between germ and somatic cells at first. Their power of direct reproduction is equal. In certain circumstances one group can be made to replace the other and undertake all its duties, and it is possible that some of the complex tumours met with in distant parts of the body, which are usually said to arise from displaced cells of the primitive germ organ, are really due to the still intact reproductive power of somatic cells. The direct reproductive power of the somatic cells, however, very soon falls away as they devote themselves to other duties, and, with the possible exception of those I have just mentioned, no tumour bud that grows from somatic cells ever attains a high stan-

dard of organisation. They may be formed of tissues, more or less well developed, heaped together with a certain amount of order or arrangement, but they are never made up of structures such as organs.

The classification of the tumours that grow from the somatic cells depends upon the classification that is adopted for the tissues themselves. Every tissue has its own kind of tumour, just as it has its own kind of structure. However much one tumour resembles others in general arrangement, it differs from them just as the parent organ differs from the rest. Under the term adenoma, for example, are included all tumours built on the lines of glandular tissue; but those that grow from the parotid gland are as different from those that grow from the mammary gland as one organ is from the other. So it is with the tumours that grow from the various forms of connective tissue. They have certain general features in common like the structures from which they spring, but those that grow in one part of the body behave quite differently from those that grow in another, though we may not be able to detect the cause of the difference. And the same thing is true of what are called malignant growths. Not only is the cancer of every organ in the body different in

clinical significance from the cancer of every other organ, but the cancer of each individual is as different from the cancer of all other individuals as his constitution is from theirs. Two cases of cancer involving the same organ may appear to be exactly alike, but it is impossible from a knowledge of the one to make certain what will be the course of the other. Every organ in the body has its own kinds of tumour, and groups founded upon a similarity in general structure must be regarded merely from the point of view of convenience and not as a system of classification.

Moreover, there are many organs, such, for instance, as the thyroid and prostate, the tumours of which are so peculiar that they can scarcely be brought into a general scheme.

The clinical character and the rate of growth of these tumours, both of those that spring from germ cells and those that spring from somatic cells, depend upon the degree of maturity already reached by the cell from which the tumour had first branched off upon its independent career. It makes no difference whether the parent is a connective-tissue corpuscle, or an epithelial cell in a secreting gland or in an ovarian follicle. If the parent cell has already progressed so far as to have acquired distinctive characteristics, the bud

that grows from it will imitate it more or less closely; growth will be slow, and as the size of the tumour increases, surrounding structures will be pushed upon one side, out of the way. Adenomata, for instance, originate as buds built of cells that resemble but are never so perfect as those of the parent gland. But if, on the other hand, the parent stock is still in the embryonic stage of life, composed of young rapidly growing cells, such as those that spring up among older ones to replace what is worn out or lost, the cells that form the tumour bud will be of a corresponding embryonic type, capable of multiplying with all the energy of embryonic cells and of spreading into and invading everything around.

If the organism were represented as a single stem, dividing into two great branches, one composed of germ cells and the other of somatic cells; and if the former of these branches were represented as dividing, in its turn, into two, one for the ovary and the other for the testis, and the latter into a number as countless as the different organs and tissues of which the body is composed, gemmation tumours would be represented as aberrant buds springing at any point from cells in the parent stem, or one of its divisions. Each bud would develop in the same direction as the branch

on which it grew, but would never attain the same degree of perfection. The cells that lie at the base of the bud would determine the structure of the tumour. A bud, for example, that grew from the parent stem would become almost as complex in structure as the nearest natural branch, while one that grew from a topmost twig would be composed only of the simplest tissues. But the character of the tumour, whether it was malignant or not, would depend, not upon the height to which the branch had grown before the bud came off, but upon the degree of maturity of the cells at the base of the bud. The bud that would form an innocent tumour if the parent cell had nearly reached maturity will grow into a malignant one it it is still in the embryonic stage. Every innocent tumour has its counterpart among malignant growths. Innocent and malignant spring alike from the same cells, but in the one case the parent has already reached, or nearly reached, maturity; in the other it is still in the embryonic stage, with all the embryonic vigour of growth unimpaired.

The Conditions that lead to the Production of Tumour Buds

In the more highly organised animals the power of direct reproduction remains latent throughout

life. It gives no indication of its existence, so long as conditions are normal. The germ cells devote their whole energy to the sexual method, which sooner or later supersedes the direct one. The somatic cells are too deeply engaged with other kinds of work to concern themselves with reproduction of any kind ; and the original method falls into the background. The sudden awakening that leads to the production of a tumour bud must be due either to the suspension of some influence that normally acts as a restraint upon reproduction, or to the action of a stimulus sufficiently strong to rouse it into activity, or, with greater probability, to the two working together.

Development as the restraining influence.— Looking back upon the evolution of the race, as it has grown up step by step, there can be no question that one of the main forces, if not the main one, that restrains and controls the function of reproduction is the advance of organisation and development. The higher the race in the scale of organisation, the lower its reproductive power.

What is true of the evolution of the race is equally true of the evolution of the individual and of the tissues that compose it. The range of direct reproduction steadily diminishes as organisation advances. It diminishes as one race that is more

highly placed in the scale of organisation succeeds another, and it diminishes as tissues become more highly specialised, until at last in the most highly specialised reproduction may not take place at all. The advance of development is the restraining force, in the absence of which growth (increase in size) and reproduction (increase in number) are limited only by the supply of food and by surrounding conditions. The arrest of development sets growth and reproduction free.

So long as development continues as it should, work is properly done, growth and reproduction never break bounds, and the tissues never give birth to the irregular structures known as tumours. If the influence of development is removed, control over growth and reproduction is lost. The latent power of the tissues is set free, and all that is needed is a stimulus such as local irritation to start it on its course. The tissue cells at once begin to increase and multiply, and a tumour bud is born like its parent in structure, capable of growing to any size, if it can get supplies, but incapable of attaining a higher degree of development, for the progress of development has been arrested.

The chemical basis of development.—Now development, like growth, is the outcome of the

chemical changes that take place in living tissues —the changes upon which their working and their life depend. This is acknowledged in the case of growth. Foreign substances come into contact with a living cell. They are absorbed by it and broken up in it by catalytic agents. The products of this catalysis are built up again in a different combination, and if the addition exceeds the consumption the result is, first, increase in size, and then, if circumstances are favourable, increase in number, each newly formed cell possessing the same power as the parent of which it once was part.

The same thing is true of development. Development, like growth, is the outcome of chemical changes that take place in the living cell, but there is this difference, that while growth depends upon the maintenance of all the reactions in their relative proportions, development depends upon the predominance of one. Development is the result of one of these chemical reactions, or rather of one series of them, being carried on by one part of the body in excess of all the rest for generation after generation. Division of labour means that every part of the body has to undertake a special kind of work. Special work entails a special chemical reaction or series of reactions. The more

thoroughly the work is done, the more completely does this special reaction predominate over all the others at that particular spot. This, continued in the same group of cells for generation after generation, of necessity involves progressive modification of chemical constitution and of structure, or in other words development.

The layer of cells, for example, on the exterior of the organism, always exposed to foreign influences, becomes modified in course of time. They become harder and more resistant, keratin or some similar substance forms in them; and as generation succeeds generation and a similar modification takes place in each, at last an outer protecting layer is developed characteristic of that particular kind of organism. The same thing is true of the cells that line the digestive tract. Their special work, or one part of it, is the manufacture and discharge of catalytic ferments. The chemical reactions upon which their working depends have been gradually evolved in the course of ages from simpler ones of the same kind. According to Ehrlich and others the process of chemical evolution is still going on. New ferments are being formed, even at the present time, to deal with new conditions, and structure and arrangements are modified accordingly. So it is with other

tissues and other parts of the body—those, for example, that are concerned with the transmission of impulses from one organ to another. Special work everywhere involves the evolution of special chemical reactions; and as generation succeeds generation and the reactions become better adapted to the end in view, the structure and arrangement of the part become modified to suit.

The development of a tissue or of an organ, in other words, is the outcome of the persistent cultivation of a special series of chemical reactions, brought into existence by the special work assigned to that particular part of the body. At the beginning these reactions were of the simplest character. As time passed and the race was built up, so step by step these chemical reactions were built up with it until they have reached their present degree of complexity. All development, like growth, is ultimately the outcome of chemical changes in the tissues, in part the chemical changes that have taken place in days gone by, the results of which have been handed down from generation to generation, in part the results of those changes that take place in the tissues themselves at the present day, and anything that interferes either with the inheritance of the products of past chemical changes, or with the effects of present

ones, interferes with, and checks or stops, the advance of development.

The Arrest of Tissue Development

The effect of such an arrest of tissue development depends upon the particular stage at which it takes place. The development of the individual is an epitome of the development of the race. This is true not only of the individual, but also of the tissues that compose it. All the tissues of the body, in the course of their development, epitomise the changes that took place in their ancestors during the evolution of the race. If the development of any tissue is arrested at any point, so that it remains on a plane which was normal for some of its predecessors, that tissue retains and can exercise (supposing conditions are favourable) all the powers those predecessors possessed, no matter how far back they may have been in the evolution of the race.

The tissues, for example, are able to exercise the power which was enjoyed by many of their remote ancestors, of throwing off buds capable of independent growth. In those days the buds developed into organs or limbs, or even sometimes into complete individuals. Now, in the abnormal conditions in which they are placed, they can only grow

into tumours, shapeless masses, the tissues of which present a general resemblance to those of the parent, capable of unlimited increase, but, incapable of progressive development, for development has been stopped.

All that is needed is some exciting cause, mechanical or chemical, to give the growth a start.

So little is known of the intimate nature of the chemical changes that take place in the tissues, that it is not easy to cite instances in which the failure of any particular chemical reaction has led directly to the cessation of development and the birth of a tumour. There are, however, many isolated facts that point in this direction. One of these relates to the occasional disappearance of tumours. It is well known that tumours, especially those of an embryonic type, sometimes stop growing, diminish in size, and even disappear under the influence of remedies which can only act through the medium of the general nutrition. Cancer of the breast, for example, has been known to shrink in size and even to disappear after oophorectomy, and sarcoma after the administration of thyroid extract. The same thing occasionally happens without special treatment of any kind, perhaps more frequently than is usually believed. At least it is difficult in any other way

to account for the single successes of queer remedies recorded from time to time, apparently in perfect good faith, which can never be repeated. In the case of most of these it is not possible to say how or by what means the remedy acts; but in some it is almost certain that the effect is due to the reagent entering into chemical combination with the living substance of the tumour cells, and thereby altering the reactions that take place in them. Arsenic, for instance, administered internally sometimes causes glandular growths to recede and almost disappear. Then, only too often, after a little while, the growth begins to increase in size again, and now the same drug, even in far larger doses, has absolutely no effect. The same thing is true of Coley's toxins in cases of sarcoma. It is not uncommon to find that a sarcomatous growth diminishes greatly in size after a few injections, without disappearing altogether, and then starts growing again in a form that is absolutely resistant even to much larger quantities. The tumour cells, in other words, have acquired immunity and have become arsenic-fast or toxin-fast, as the case may be, just as Ehrlich has shown the spirochæta can, and for the same reason—the drug has entered into chemical combination with some element in the substance of the growing cell.

Another of these facts, in many ways even more striking, relates to the production of tumours. It is well known that the continued employment of certain substances, in industry as well as in medicine, is liable to be followed by the growth of certain kinds of tumours. The substances themselves are not the immediate cause of the growth. There is often an interval of years between their administration and the appearance of the tumour. But they initiate such changes in the nutrition of the tissues that when irritation of any kind leads to the rapid production of a large number of young cells, some of these cells stop short of the normal standard of development and form the nucleus from which a tumour bud begins to grow. This has long been known in connection with arsenic. The late Sir Jonathan Hutchinson was the first to lay emphasis upon the fact that the prolonged internal administration of arsenic sometimes led to the development of multiple tumours of the skin. The nutrition of the skin becomes affected; its texture becomes altered, and then, at some spot where continued irritation leads to the rapid production of a number of young cells, epithelioma develops.

A closely similar course of events has been described in connection with some of the anilin dyes,

only in this case the tumours do not involve the skin but the urinary organs, and assume different forms according to their origin. Rehn, in 1906, had already collected more than thirty cases of workers in fuchsin who were suffering from some form of tumour of the bladder. Leuenberger has collected many more and has shown that in Basle the deaths caused by tumours of the bladder in the years 1901–1910 were thirty-three times more common among the workers in anilin colours and similar substances than they were among the rest of the male population; and that more than half of the cases of tumour of the bladder observed in the last fifty years in the male surgical clinic at Basle came from dyers and those engaged in anilin dye works. In the majority of the cases observed by Leuenberger himself the growth was a carcinoma; but in some it was a sarcoma, and in others it was mixed. Some grew in the bladder, others in the kidney and ureter; and, what is of peculiar significance, in some instances the growths did not make their appearance, or at least cause symptoms, until years after the worker had left his employment. A similar condition of things has been recorded of the workers in the cobalt mines of the Schneeberg, only in this case the growths, which are equally

varied in their character, are met with in the lungs.

The tumours that so often follow the continued application to the skin of soot, tar, paraffin, and the like, arise in a similar manner. Some substance is absorbed which, in course of time, affects the nutrition and functional activity of the skin, so that it becomes harsh and dry to the touch. The cells that compose it cannot carry on their work as they should. Their development, which depends upon the chemical changes that take place in them during their work, remains imperfect. It comes to an end before it should, while the cells are still in a stage that was perfect for their remote ancestors, but should have been only a transition stage for them, and, as a consequence, at a time when they are still capable of exercising the powers those ancestors possessed. The result when they are irritated in some way is the formation of a bud, like the buds that were thrown off from time to time by their ancestors, capable of independent growth and composed of cells, the rate of whose growth and multiplication depends upon the maturity of the parent-stock at the moment. If the affected cells have all but reached adult age before the interference is felt, the buds that grow from them are all but adult too. The

tumour is composed of tissues that resemble those of the normal skin. But if, owing to irritation, whether it is mechanical or chemical or due to the action of living organisms, there is a great increase in the proportion of young rapidly growing cells, and the development of these is checked in their youth, the buds that spring from them resemble them, and then the tumour increases rapidly and spreads wherever it can.

These tumours, in short, irrespective of their clinical characters, are the product of the innate power of asexual reproduction present in some measure in all tissues, except perhaps the most specialised of all. So long as the development of the tissues continues to be normal, growth and reproduction are normal too. But the development of the tissues is based upon special chemical reactions, which have been evolved in the course of ages and are still being evolved. If these reactions are interfered with, for example, by some strange element such as arsenic entering into chemical combination with the substance of the cutaneous cells, work is interfered with, so that the skin becomes harsh and dry; development is checked, leaving the surface glazed and rough; and the young cells that are formed from time to time to replace those that are worn out, instead

of attaining their true standard remain upon a lower plane of evolution—a plane that was normal for their ancestors—with the same powers of reproduction and bud formation that those ancestors possessed, and only require some local stimulus to start them on their career of growth.

In the illustrations I have given the interference with the nutrition and the chemical reactions of the tissues has been caused by the slow continuous working of substances introduced into the body from without. Some have entered through the digestive tract, others through the lungs, and others again through the skin. Whether substances capable of causing a similar effect can be produced in the body is not known. (The alimentary canal, so far as concerns the formation of toxins, is outside the body.) There are many things that suggest it, such, for example, as the occasional disappearance of tumours under the influence of thyroid extract; the rapidly increasing incidence of tumours as age advances and the power of development recedes; the occurrence of multiple and of symmetrical tumours, and the tendency of the same kind of tumour to occur in members of the same family at about the same time of life, or in consecutive generations; but there is no evidence comparable to that furnished

by the action of arsenic and the other substances I have mentioned. Nor is it likely there will be until we know far more of the chemical changes that take place in living tissues than we do at present.

The Inheritance of Gemmation Tumours

The question whether tumours can be inherited or not is best answered by a consideration of their mode of origin. It is difficult to imagine that characters often acquired late in adult life can be transmitted from parent to offspring. On the other hand it is well known that certain kinds of tumours commonly occur in several members of the same family, not infrequently at approximately the same time of life.

Tumours that grow from cells of the germ organ or its derivations can hardly be transmitted by inheritance. It does not seem possible that a cell which, owing to its development having been arrested, is able to give birth to a tumour bud by a method of reproduction peculiar to its ancestors can afterwards be fertilised and develop as if it were normal. So far as that particular cell is concerned, there can be no second generation. If a second generation is formed it must be descended

from some of the other cells, the development of which has not been interfered with.

The same thing is true of tumours that grow from the somatic cells. There can be no such thing as direct inheritance from somatic cells, for they have no descendants. The somatic cells, when once a certain point, quite early in the life-history of the more highly organised animals, has been reached, cease to have anything to do with the reproduction of the race. The somatic cells and all the organs and tissues formed from them, no matter how complete or how highly specialised they are, exist for the generation only. Their purpose is achieved when once the new germs are launched by the germ organ. They may die at once, as in the case of many insects where the procreative act is followed immediately by death; or if it is for the benefit of the race, if they possess qualities that will be of advantage to the coming generation in the battle of life, as for example in the case of mammals, they may be continued a little longer; but these never have descendants of their own. The protective and supporting framework built up out of the somatic cells to serve the generation perishes with the generation, and transmits nothing by direct inheritance to the next; the continuity of the germ is preserved, to

produce in each generation a framework for its own support, moulded, with more or less of modification, on the plan of those that have gone before.

It does not follow, however, that because the somatic cells have no descendants of their own, changes that occur in them are without influence upon the next generation. The influence may be indirect, but it is very far reaching. The germ cells are supported and maintained entirely by the somatic cells. It is the special work of the somatic cells, and every structure formed from them plays its part. No change, such as that which attends the growth of a tumour, can take place in any structure formed from the somatic cells without affecting the growth and nutrition of the germ cells and of the generation developed from them. To what extent it can do this depends upon the degree of development the germ cells have attained already. If the change occurs at a sufficiently early period in the life-history of the individual, before the germs are fully developed, the effect may be so great as to cause them to reproduce the altered features in the somatic cells that spring from them. The germs have grown up under the influence of structures, normal or otherwise, developed from the somatic cells of the

parent; and when they begin to divide and multiply, the somatic cells to which they give birth are stamped with the impress of the altered conditions under which the parent lived.

Such an effect as this is only possible if the change occurs at a very early period of existence, while the germs for the next generation are being formed. Tumours that grow from somatic structures, with very few exceptions, make their appearance far too late. The germs for the next generation are already well developed and often detached from the parent body long before most tumours begin to grow. They cannot therefore affect the nutrition of the germ cells or be transmitted either directly or indirectly to the offspring. But though this is true of the tumours themselves, it is far otherwise with the arrest of tissue development, the condition that underlies the production of tumours, without which no stimulus, however active it may be, is of any avail. The development of the tissues may be arrested at any point. It may be arrested at the very beginning, long before the germs for the next generation are developed, and their growth and nutrition may be influenced to such an extent that when they in their turn divide into germ and somatic elements, the development of the corresponding somatic

cells is arrested at the same point, and at the same time. Tumours cannot be transmitted by inheritance, but the condition that is essential to their production can be. Such a condition may be handed down through generation after generation, though in the absence of the necessary stimulus it may never result in actual tumour growth.

CLASS II

TUMOURS DUE TO DEFECTS IN STRUCTURAL DEVELOPMENT

THE tumours of which I have spoken hitherto are due to the action of local irritation upon tissues which, owing to their development having been arrested, remain in possession of a high degree of reproductive power, such as would have been normal in the case of some of their remote racial ancestors. Besides these, there is another class of tumours, not nearly so large, due not to arrest of development of the tissues, but to the imperfect carrying out of certain structural changes that should have been completed in the course of development. They differ from those already described in that they do not originate as buds capable of leading an independent existence. They

belong to the same generation as the structure from which they grow, not to the succeeding one.

Irregularities of development lead to the formation of various kinds of tumours, such, for example, as inclusion dermoids, but the most important are those that are caused by structural defects.

Development implies not only the progressive advance of tissues that are of use, but also the recession and disappearance of those that have ceased to be of use. It involves not only evolutionary changes, but involutionary ones too. Arrest of either of these may lead to the formation of tumours.

The ordinary spinal meningo-myelocele is an instance of the former. The medullary groove fails to close at the proper time, leaving an unprotected place on what will become the outer wall of the organism. As the size of the organism increases and the tissue pressure with it, this weak place is forced to yield, and the body wall is gradually pushed out farther and farther, until at last it forms a cystic tumour the covering of which is the everted floor of the medullary groove.

Instances of the latter are more common. There are many organs present in early life of which no trace is to be found in later years, and many more of which only some small portion persists because

it has been possible to adapt it to other purposes. Disappearance of structures that are no longer of use is part of the normal development of the body. If development is arrested these structures persist. Sometimes they remain stationary and do no harm; but they may continue to increase in size in proportion as the body increases, and to work after a fashion, and then they may grow into the most formidable tumours. Cysts developed from the remains of the hyolingual duct or the Wolffian or Mullerian ducts may not be serious, but those developed in the coccygeal region, in connection with the postanal gut, often lead to the gravest consequences.

H. K. LEWIS & CO. LTD.
136 GOWER STREET, LONDON, W.C.